CHAPTER 8

GENERAL DISCUSSION:

EFFECTS OF "NATURE" AND "NURTURE" IN VOLUNTARY ACTIVITY AND NUTRITION ON ENERGY BALANCE AND EMOTIONALITY

1. Introduction

Animals are able to travel across the environment in the attempt to overcome environmental challenges (e.g., escaping predation, climate change, etc.), or to achieve certain goals (e.g., find nutrients, fluids, partners, social interaction, etc.). In doing so, they need to combust extra fuels above the basic requirements, in order to provide energy for skeletal muscular and cardiovascular activity. The level of locomotor activity can vary tremendously between species, but also considerable individual differences can be observed within certain species. An increased level of locomotor activity may increase survival rate of animals by allowing the coverage of larger habitats. Co-adaptational changes may be needed for animal physiology, morphology and behavior to facilitate and sustain high levels of physical activity. Selective breeding for voluntary physical activity is an appropriate tool to study potential co-adaptational changes, since selective breeding for one trait could be linked to changes of several sub-ordinate traits that may determine individual variation. In this thesis, I used two lines of mice selectively bred for increased wheel running behavior and one control line created by Prof T. Garland and colleagues. The aim was to investigate in these lines of mice regulation of energy homeostasis under non-reproductive and reproductive conditions, and its contribution to perinatal programming of energy homeostasis in the offspring. Below, the main results from the different studies are summarized.

The aim of **Chapter 2** was to study behavioral consequences of selective breeding for high voluntary activity. The results demonstrated that mice with high activity levels responded differently in novel and habituated environments. In a novel environment, high activity mice were more anxious, more explorative and risk-taking suggesting that their level of carefulness, cautiousness and attentiveness was increased relative to non-selected mice. In a habituated environment, they had increased routine behavior, which probably helps them to sustain their physical endurance activity.

In **Chapter 3**, activity selected and control mice were subjected to feeding either a carbohydrate-rich/low-fat (LF) or a 60% high-fat (HF) diet and temporal changes in energy balance characteristics over the daily cycle were studied. Compared to controls, physically active mice had an increased locomotor activity and increased energy expenditure (particularly in the HF diet condition) during the dark phase. In active males, the latter was particularly due to increased carbohydrate oxidation. In contrast, active females showed a strongly increased fat oxidation, particularly on the HF diet. Since active females started ingesting their bulk food later in their active phase, this might make them more prone to metabolic insufficiency. In view of their leanness, their LF diet preference over the HF diet was surprising, but may be viewed as a result of metabolic sensors potentially signaling shortage of intermediary citric acid metabolites necessary for fat oxidation, and refers to old adage that "fats burn in the flame of carbohydrates".

In **Chapter 4**, control and activity selected mice were subjected to a LF or a 40% HF diet with added refined sugars, and the effects were studied on parameters related to energy balance and emotional stress. The results showed that the active lines were HF diet obesity resistant, with increased food intake, similar absorption rates and higher non-exercise

thermogenesis (NEAT) than their randomly bred controls. While activity selected females had a higher anxiety level in the LF condition than controls, this effect reversed on a HF diet, without concomitant changes in plasma levels of corticosterone. Since active lines again had a lower HF preference than controls, these data may be viewed such that the activity lines, and in particular the females may improve their mood on a HF diet, without necessarily liking the HF diet more than control mice.

In **Chapter 5**, the differences between control and activity selected mice were investigated on reproductive performance during the perigestational period in relation to feeding a LF or 40% HF diet with added refined sugars. The results showed that the active lines had increased reproduction output and an increase in growth efficiency during peak lactation on the HF diet relative to controls, but had mixed advantageous effects on pup survival. Regression analysis revealed that litter size acted as a strong dependent variable, and effects of diet and line on several pup characteristics remained significant within the regression analysis.

In **Chapter 6**, we aimed to study the long-term consequences of feeding HF or LF diets during the perigestational period in activity-selected mice and in their controls on energy balance regulation in the offspring. The outcomes showed that active lines are protected against the early programming effects of HF diet feeding as demonstrated by the maintenance of a lean phenotype, elevated plasma levels plasma of adiponectin, and low plasma levels of leptin and insulin. In contrast, their randomly bred controls had increased longitudinal growth, higher adipose tissue mass, and elevated insulin and low adiponectin levels. Again, regression analysis revealed that litter size the animals were born in was an important dependent factor, but with diet and line having particular effects on structural growth parameters.

Chapter 7 had two aims: A) to study the contribution of perigestational HF or LF diet feeding in activity selected mice and in controls independent of differences in litter size on reproductive performance and offspring characteristics and B) to study postnatal influences in active and control mice by cross-fostering of pups between lines. In part A) the results demonstrated that equalizing litter size to 10 pups/litter prevented perigestational HF diet effects on postnatal body weight gain in the control line, but instead caused transiently increased weight gain and increased adiposity at the adolescent stage in the activity selected mice. An explanation for these unexpected results is that equalizing litters frequently needed culling down in the active lines, whereas those of the control line often needed additional pups. In this situation, the highly active mothers suddenly faced on average two pups less than they prepared for, and probably over-nourished their offspring to higher average body weights and adiposity. Controls on the other hand, had to nurse more pups than they prepared for, and this could have lead to a normalization of body weight and body adiposity levels. Effects of over-nourishment in the activity-selected lines, however, were transient and overridden by trait at adulthood.

In part B) cross-fostering experiments revealed that females of selection lines provided different postnatal environments to their offspring than control females, but also differences between activity selected lines 7 and 8 were observed. When pups were exchanged between the

control and selected line 8 mothers, pup growth was not affected. However, when pups were fostered between control and selected line 7 mothers, control pups became smaller and line 7 pups became transiently larger. The postnatal environment of selected lines, irrespective of diet, resulted in low plasma levels of insulin and glucose in control animals, overriding the prenatal (epi)genetic make-up of control offspring later in life. However, prenatal genetic make-up of selected lines could not be overridden at adulthood by a relatively rich environment of controls even in the presence of a HF diet during the perigestational period. Interestingly, growth efficiency during lactation of pups and mothers of the control line became increased on a HF diet. This was different compared to the results in Chapter 5, and may be caused by the contribution of fostered selected pups in the control litters. Furthermore, the pup loss of line 7 mothers found in Chapter 5 did not occur in the line 7 litters with fostered control pups of line 2 in the present study. This improved pup survival could indicate that pup loss in line 7 litters of Chapter 5 was the result of bi-directional pup mother interactions rather than the result of poor maternal care per sé.

2. Connecting physical activity and emotionality/personality

In nature, animals invading novel habitats and having no prior experiences with their challenges usually have increased stress levels since they do not know what to expect (e.g., of predators, climate etc.). However, they need to overcome these emotional challenges and find nutrients, water, partners etc, to secure their own survival as well as that of its progeny. As mentioned earlier, highly active animals might have an advantage to cover larger habitats, but exposure to the outside environment may require other specific qualities to improve survival. In the present thesis, highly active mice were found to be explorative, risk taking and at the same time had increased levels of anxiety in unfamiliar conditions, which may translate to a cautious and attentive behavior relative to that of control mice (Chapter 2). On the other hand, in a habituated environment, they were less attentive, and increased their stereotype, routine behavior. Although the high activity mice were more resistant to develop diet-induced obesity (DIO) than control mice when subjected to a HF diet (Vaanholt et al. 2008), the HF diet did appear to have a large influence on these personality traits in the activity selected animals just as well as did in the control mice. The directions of effects, however, were quite different between control and selected lines. In the control mice, for example, the HF diet increased anxiety in unfamiliar conditions, but the opposite was observed in the activity selected mice. These differential effects are reminiscent of opposing reports in literature that fats and refined sugars can either be comforting and decreasing stress sensitivity (Dallman, Pecoraro, and la Fleur 2005), or act as a form of background stress (Dallman, Pecoraro, and la Fleur 2005; Souza et al. 2007; Tannenbaum et al. 1997). The data in the presented studies may be interpreted such that (a trait for) physical activity acts as a lever to determine the direction of emotionality behavioral when subjected to diets differing in HF and sugar content. Congruent changes in neuroendocrine and

physiological parameters were less clear, although emotional and behavioral effects of HF diets have previously been shown to have specific neuroendocrine and physiological correlates (Steimer, la Fleur, and Schulz 1997). From a teleological standpoint, a too dramatic decrease in the level of anxiety may negatively affect chances of survival. However, without the beneficial effects of diet-induced thriftiness (i.e., which probably enables the control mice to survive upcoming periods of famine better than the activity selected mice), a trait for increased physical activity might benefit survival in well-fed conditions by augmenting agility, extraversion and fearlessness under unfamiliar conditions.

3. Life-style factors in relation to complex diseases

Besides understanding neurobiology of energy balance regulation from an adaptive standpoint, animal models with selected complex traits have also been used for understanding pathological mechanisms and treatment effectiveness of human diseases. Human studies suggest a complex interplay of life-style factors, including behavioral inactivity, "unhealthy" eating habits, in the aetiology and manifestation of disease. Again, stress might play an important role since, for example, the metabolic syndrome is found more prevalent among individuals under psychosocial pressure or chronic stress (Bjorntorp 1992; Brunner et al. 2002), and this has been associated with emotional eating, binge-eating and depression as well (Pinaquy et al. 2003). Furthermore, several reports taken together seem to suggest that a change in any of these life-style factors can bring about changes in the others, and ignite a chain reaction leading to pathology development (van Dijk and Buwalda 2008; Tsatsoulis and Fountoulakis 2006; Kishi and Elmquist 2005; Foreyt 2006). Different disciplines revealed that physical activity can be used as a preventive or corrective tool in many metabolic abnormalities and diseases (Hayes and Kriska 2008; Brock et al. 2005; Colberg 2007; Donnelly et al. 2009), as well as emotional and mental complications (Antunes et al. 2005; Budde et al. 2008; Galper et al. 2006; Kramer and Erickson 2007; Kruk 2007; Otto et al. 2007; Pearce 2008). Therefore, studying physiology and behavior in animals with complex traits for high physical activity can help to improve our understanding of the underlying mechanisms of these prevention and treatment options.

4. Physiological co-adaptations of endurance activity

Endurance exercise requires an increase in aerobic capacity and increased oxygen consumption, which is strongly related to an increase in heart-minute volume during activity. This facilitates oxygen perfusion of energetically demanding organs and increases transport of carbon dioxide and waste products away from these organs (Laughlin and Roseguini 2008; Betik et al. 2009; Baar 2009; Hickson, Bomze, and Holloszy 1977). To serve these energetic requirements, nutrients need to be taken up from ingested food and transported to the demanding organs or first being

stored in the form of glycogen or fat, and released later. Because of higher voluntary activity and energy expenditure in the selected mice, an increase in food intake behavior needs to be temporally spaced between bouts of activity across the circadian cycle. In the selected mice, this caused ingestive behavior at times when controls were not feeding (Chapter 3). Not only the amount but the type of ingested food is important to support energy utilization. In the present experiments, the activity selected mice had increased preference for carbohydrate-rich food over fat food, potentially to secure their fatty acid oxidation rate (chapter 3). A decrease in fat tissue and a shift to an increase in dry lean mass is associated with the increased rate of fat oxidation, and others have shown that this is paralleled by an increase in the number of mitochondria and oxidative muscle types (Guderley et al. 2006; Guderley et al. 2008; Houle-Leroy et al. 2000). Since the increased nutrient delivery during physical activity can be caused independent of insulin (Hamilton and Booth 2000), the level of the metabolic hormones insulin and leptin, which promote glucose uptake and lipid storage, are less important under conditions of chronic exercise. The high level of adiponectin, on the other hand *is* important since this hormone has been shown to stimulate mitochondrial biogenesis and to augment fatty acid oxidation in skeletal muscle (Yamauchi et al. 2002; Civitarese et al. 2006).

Over the last decades, environmental factors largely changed and favored consumption of comfort foods, containing high percentages of saturated fats and/or sugars. In order to maintain body weight and energy homeostasis, this "nutritional challenge" should be balanced by a higher intensity of physical activity, to reverse metabolic abnormalities. The mechanism by which physical activity can reverse these abnormalities is related to an increased non-exercise thermogenesis (NEAT) (chapter 4). Increasing sports during leisure time may be less effective, since this may lead to compensations by resting more (McCrady and Levine 2009; Levine 2007). A high level of NEAT, however, may clear triglycerides and increase skeletal muscle oxidative capacity as well. According to the findings in Chapter 3, this might stimulate carbohydrate preference, allowing that the dietary or stored fat is burning in the flame of carbohydrates (chapter 3).

Although leanness and increased aerobic capacity as a result of endurance training are not associated with a clear reduction in basal metabolic rate (Bouchard, Depres, and Tremblay 1993), there is however evidence that it increases metabolic efficiency in humans as well as rodents (Schrauwen and Hesselink 2003; Amati et al. 2008). This increased metabolic efficiency and nutrient utilization gained by increased physical activity could have been beneficial for growth efficiency during the reproduction stage, when energy requirements are sustained far above normal requirements. Indeed, highly active females were able to reallocate their energy, which was used normally to sustain physical activity to their offspring by decreasing their physical activity levels. The latter may be facilitated by hormonal changes that occur during lactation. Human studies also supported the notion that moderate exercise training during pregnancy and lactation is beneficial both for mothers and offspring development later in life (Gavard and Artal 2008; Impact of physical activity during pregnancy and postpartum on chronic disease risk2006).

5. Early life influences

Early life experiences are relevant in the context of maintenance of adult health, or disease development later in life. The mechanisms have yet to be resolved, but probably include gene-environment influences. The "thrifty genotype hypothesis" explains that genetic factors only predispose individuals to diseases but environmental factors determine phenotypic expression whether the disease becomes manifest or not (Neel 1999). For example, a thrifty gene enables the organism to store nutrients during times when food is scarce, but in times when it is plenty it leads to excess energy storage and metabolic diseases. In this way, comfort foods could have maladaptive consequences on offspring development and later in life, when availability of food remains and psychological stressors are chronic (van Dijk and Buwalda 2008). According to Chapter 6, palatable high fat/sugar feeding during the perinatal stage causes exaggerated weight gain and adiposity with a larger susceptibility in male offspring than in female offspring (chapter 6). The duration of the diet supply also determines the intensity of derangements (chapter 5), and probably depends on the critical timing of postnatal development of feeding circuits in the central nervous system (Bouret and Simerly 2006). When the maternal HF diet is supplied to the pups via nursing (i.e., feeding via the milk), the offspring show less severe consequences of the maternal HF diet than when they start eating from it by themselves. For example, in the case of a perigestational HF diet condition strictly via the milk, offspring developed increased growth with a proportional increase in fat mass. Nutritional effects on postnatal development in rodents are also dependent on the size of the litter beyond the type of diet. Small litter offspring are more prone to develop metabolic diseases together with elevated plasma insulin and low levels of adiponectin even without disproportional fat mass increases (Chapter 6). On the other hand, the trait for high voluntary activity seems to protect against the deleterious effects of perinatal HF diet feeding with an increased water intake and adiponectin levels. These effects facilitate cell metabolism and energy expenditure (Chapter 6). Although cross-fostering pups between mothers of different lines caused transient changes at adulthood, the trait of high physical activity was not influenced by postnatal environmental conditions, meaning that the protective function of a high activity trait was determined by prenatal (epigenetic) factors (chapter 7). In contrast, control mice fostered by activity selected mothers were sensitive to postnatal influences and developed similar growth, glucose and insulin levels as selected mothers. This is in line with studies showing that maternal physical activity positively influences offspring metabolic- and mental development, and promotes long-term benefit against chronic diseases in the offspring (Impact of physical activity during pregnancy and postpartum on chronic disease risk2006; Gavard and Artal 2008; Larson-Meyer 2002). The task that lies ahead of us is to unravel the mechanisms behind these interactions.

6. Mapping genotype after phenotyping selectively bred animals

Despite our vast knowledge on the beneficial effects of physical activity, and the efforts of healthcare officials, medical specialists, and government programs to promote it, many people still remain physically inactive, and have an increased risk to attract metabolic diseases. Apparently our understanding in the treatment of complex diseases falls short. Studying complex traits such as those of mice selectively bred for increased running wheel activity may provide novel directions for research (see: http://biology.ucr.edu/people/faculty/Garland/Experimental Evolution Publications by Ted Garland.html). One of these directions should acknowledge the genetic underpinnings of differences in expression of phenotypes. The level of physical activity has been shown to be determined by many (heritable) genes. More than 214 genes and quantitative trait loci (QTL) have been mapped in humans for performance and health-related phenotypes (Bray et al. 2009), including linkages to physical activity levels (Simonen et al. 2003; Cai et al. 2006). Although the map is exhaustive for currently published accounts of genes and exercise associations and linkages, there are undoubtedly many more gene-exercise interaction effects that have not even been considered thus far, reported by Bray et al (Bray et al. 2009). Recently, the work of Leamy et al provided evidence that epistatic genetic interactions (i.e., when an allele in one locus masks the expression of an allele at another locus) contribute significantly to the variation in physical activity (Leamy, Pomp, and Lightfoot 2008). In other studies, epistatic combinations were found between physical activity and body weight (Leamy, Pomp, and Lightfoot 2009a; Leamy, Pomp, and Lightfoot 2009b), running distance and duration of running (Leamy, Pomp, and Lightfoot 2008; Lightfoot et al. 2008), litter size and maternal performance (Peripato et al. 2002; Peripato et al. 2004). Moreover, some of the QTL discovered for physical activity had pleiotropic effects (i.e., when a mutation of a single gene causes changes in multiple independent phenotypes) on several physical activity related traits in mice selectively bred for high voluntary wheel running (Nehrenberg et al. 2009). Finding these "hot-spots" and how (physiologically/nutritionally or perhaps pharmacologically) and when (i.e., perinatally, during adolescence, or at adulthood) to target them would be of major interest, and could eventually contribute to improvement of health of people in our society.

7. Epilogue.

In modern societies, the competitive and "fast" life-style causes an increase in stressful situations for which physical actions (fight/flight) no longer serve proper solutions. The parallel rise in the availability of comfort foods and automation/industrialization results in multidimensional metabolic diseases. Indeed, in 2005 the World Health Organization estimated the number of obese people worldwide to be 400 million, and they project that in 2015 the number will be as high as 700 million. Obesity is associated with several diseases, for example diabetes mellitus type II, cardiovascular diseases, some types of cancer and musculoskeletal disorders. Cardiovascular

diseases already have the highest death toll and this will continue to rise with the increasing number of people with obesity (World Health Organization 2005, http://www.who.int/). Besides being harmful for health and liveability, the increase in the prevalence of metabolic diseases is also a big economic burden to society. A study by The Conference Board has estimated the costs of obesity in the US to be around $100 billion (The Conference Board, 2008, http://www.conference-board.org/webcasts/describe_wc.cfm?ID=1373). The results described in this thesis may help to understand the protective and preventive nature of physical activity on the growing epidemic of obesity and its related diseases. This not only applies to individuals at adulthood, but particularly to their offspring. Although Westerterp and Speakman argued that human weight gain and obesity over the last decades was not the result of a reduction in energy expenditure, but caused by an increase in energy intake (Westerterp and Speakman 2008; Westerterp and Speakman 2008), healthy daily habits, such as a high degree of physical activity, dietary choice and avoiding anxiety and stress, could perhaps be imprinted during early life conditions. The need for parents to recognize the importance of physical activity and diet during early perinatal development could be supported by widespread means of education.

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